

## **Guideline for Antiviral Drugs**

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**Pandemic Influenza Experts Advisory Committee**

# Guideline for Antiviral Drugs

## Distribution adjustment

### Before outbreak occurs in Japan

- Instruct medical institutions and wholesalers not to return antiviral drugs.
- Advise medical institutions and local residents not to purchase antiviral drugs unnecessarily.

### After outbreak occurs in Japan

- Prefectural governments shall bolster intelligence on the number of reported patients and status of drug use at each medical institution.
- Instruct wholesalers to focus the marketing of drugs to designated medical institutions and high-fever outpatient departments.
- Prefectural governments shall publicize abusive buyouts of antiviral drugs by medical institutions.
- Prefectural governments shall distribute stockpile drugs to designated medical institutions through wholesalers. Prefectural drug stockpiles should be used first, and national stockpiles should be used to make up for shortages at under-stocked regions.

## Administration

### Preventive administration

- Provide antiviral drugs to prevent infection during the strategic early response period and in cases in which unvaccinated health care workers will be in close contact with (suspected) patients without sufficient protection.

### Normal influenza treatment

- Physicians shall refrain from administering antiviral drugs to patients who have manifested symptoms for over 48 hours, or to healthy adults who are unlikely to be infected by pandemic influenza.

### In the case of explosive outbreak

- In principle, antiviral drugs shall be administered within 48 hours of manifesting symptoms. Hospitalized patients in serious condition shall be of the highest priority.
- The prioritization of administration to outpatients shall be modified according to the characteristics of the actual virus.

### Relenza (zanamivir)

Used if the virus is found to be resistant to Tamiflu (oseltamivir) but sensitive to Relenza

# Guideline for Antiviral Drugs

## 1. Introduction

Based on the Pandemic Influenza Preparedness Action Plan, enacted in December 2005, the Government of Japan plans to complete the stockpile of oseltamivir phosphate (product name: Tamiflu) required to treat 25 million persons by the end of FY2007, combining the stocks and distributions of the central and prefectural governments. The abovementioned amount of planned stockpile is based on the number of individuals who will consult medical institutions, estimated using the CDC model, assuming that 25% of the national population will get infected by pandemic influenza. Stockpiling by the central and prefectural governments is in progress toward the abovementioned goal.

These guidelines provide instructions on distribution adjustments of Tamiflu, effective use of stockpiled Tamiflu, the priority of administration, etc. in Phase 4 onwards, where pandemic influenza occurs in Japan.

## 2. Distribution adjustments of antiviral drugs

If an influenza pandemic occurs, it is necessary to supply an adequate amount of Tamiflu to those infected. Appropriate distribution adjustments are necessary to avoid buyouts of Tamiflu by specific medical institutions and distributors, and a resulting shortage of distribution, price rise due to abusive transactions, and/or, in the worst case, social chaos due to riots etc. by citizens demanding Tamiflu.

### (1) Before outbreak occurs in Japan

- Prefectural governments will establish a committee on antiviral drug distribution comprising of local medical associations, drug wholesalers, scientists, health center officials, etc., as in the case of seasonal influenza. The committee members will discuss how to establish/maintain a stable supply of Tamiflu and related issues in the case of pandemic influenza outbreak, and determine and implement the following:
  - Establish a scheme capable of identifying the inventory status at local drug wholesalers and medical institutions, thereby enabling the governing prefectural government to collect information on the use and stocks of Tamiflu at medical institutions during the outbreak of seasonal and pandemic influenza;
  - Decide on supply adjustments in the case of Tamiflu shortage; and
  - Establish rules for releasing Tamiflu stockpiles
- The locations of Tamiflu storage shall not be disclosed, and shall be guarded and controlled strictly by the prefectural governments.

- The central and prefectural governments will thoroughly disseminate the following points to medical institutions and local residents.
  - The central and prefectural governments have sufficient stockpiles of Tamiflu in the event of a pandemic. Medical institutions and local residents should not panic but respond calmly if a pandemic occurs.
  - To avoid potential shortage of market distribution, no individual or entity shall buy out or otherwise procure more Tamiflu than necessary, The return of excessive stocks of antiviral drugs remaining after the end of pandemic is not admitted. The central and prefectural governments will publish the names of medical institutions who are considered to have conducted abusive buyouts or similar abusive actions.

**(2) After outbreak occurs in Japan**

1) Measures to be taken by all prefectural governments:

- The locations of Tamiflu storage shall be guarded and controlled strictly by the prefectural governments.
- Prefectural governments will repeatedly disseminate the following points to medical institutions and local residents.
  - The central and prefectural governments have sufficient stockpiles of Tamiflu in the event of a pandemic. Medical institutions and local residents should not panic, but respond calmly if a pandemic occurs.
  - To avoid potential shortage of market distribution, no individual or entity shall buy out or otherwise procure more Tamiflu than necessary,. The return of excessive stocks of antiviral drugs remaining after the end of pandemic is not admitted. The central and prefectural governments will publish the names of medical institutions who are considered to have conducted abusive buyouts or similar abusive actions.
- Following the occurrence of an influenza pandemic in Japan, the prefectural governments will bolster intelligence on the numbers of patients reported under the Infectious Diseases Law, as well as the status of drug use, at each medical institution, and monitor buyouts of Tamiflu by specific medical institutions.
- Prefectural governments will provide strict guidance to all medical institutions that experience a shortage of Tamiflu. If they do not follow the guidance, purchase additional supplies in large amounts, or take other malicious actions in response to buyouts, the name of the institution in question will be announced (to where?).

2) Measures to be taken by prefectural governments where an influenza pandemic occurs

- In prefectures where an influenza pandemic occurs, medical services to (suspected) pandemic influenza patients will be provided only at designated medical institutions for infectious diseases and medical institutions with high-fever outpatient departments (hereafter collectively referred to as “designated medical institutions”), as designated by the relevant prefectural governments.

Therefore, the relevant prefectural governments will request non-designated medical institutions to refrain from placing orders for distributed Tamiflu so that Tamiflu can be predominantly distributed to designated medical institutions. The governments will also instruct drug wholesalers to deliver Tamiflu only to designated medical institutions.

- When Tamiflu inventory in distribution drops to a certain level, the governments will [release]??(to who?) prefectural stockpiles and deliver Tamiflu to designated medical institutions through authorized wholesalers. Administration of Tamiflu will be [first concluded]?? at designated medical institutions to prevent the spread of infection. The prefectural governments will periodically report (1) the amount of remaining stockpiles and (2) the amounts used to the central government.

3) Measures to be taken by the central government after an influenza pandemic occurs

- The central government will monitor the status of patients and use of stockpiled Tamiflu nationwide. If Tamiflu is likely to run short, the central government will [release]??(to who?) the national stockpile and deliver required replenishment of Tamiflu to prefectural designated medical institutions through authorized wholesalers.

### **3. Administration**

#### **(1) Preventive administration**

- It is extremely important to contain infection at an early stage of the influenza pandemic through preventive administration of Tamiflu, as recommended by the WHO. Therefore, preventive administration will be performed as part of a strategic early response to prevent the spread of infection.
- It is also important to protect health care workers etc. from infection, manifestation of symptoms, and falling into serious conditions, so that medical services can be sustained and wide-spread infection will not result. Preventive administration of Tamiflu will be provided to unvaccinated health care workers etc. who have come into close contact with (suspected) patients without sufficient protection. If such health care workers etc. have previously received tested vaccination, preventive administration will not be provided. If such vaccinated individuals manifest a high fever or other symptoms, they will be immediately treated with Tamiflu, even before a diagnosis is confirmed.
- Preventive administration will be organized by physicians at local public health centers, with the cooperation of regional medical associations as necessary. In principle, the national stockpile will be used for preventive administration. However, in the case of emergency, prefectural stockpiles may be used first, and later replenished from the national stockpile.

- Preventive administration as described above is not necessarily approved under the Pharmaceutical Affairs Law. Individuals (including their guardians in the case of children) will be sufficiently informed of this point, and receive administration only after consent is given.
- Preventive administration is conducted as a part of strategic early response and aims to prevent the spread of infection while the influenza pandemic is occurring in limited geographical areas. Therefore, if infection by pandemic influenza spreads, or if drug stockpiles for preventive administration drop below a certain level, the central government will instruct prefectural governments to suspend or discontinue preventive administration as a part of strategic early response, so that the remaining drugs will be used effectively and efficiently.
- If the level of remaining drug inventory drops further, the central government will instruct the prefectural governments to refrain from preventive administration to health care workers, and to treat (suspected) patients with Tamiflu as soon as they manifest symptoms, before diagnosis is confirmed.

**(2) Treatment of seasonal influenza during outbreak of an influenza pandemic**

- Even during the outbreak of an influenza pandemic, the elderly, children, and individuals with underlying diseases may fall into critical conditions due to seasonal influenza, and therefore may need treatment with Tamiflu.

On the other hand, healthy adults are generally unlikely to fall into critical conditions due to seasonal influenza. Therefore, physicians may refrain from administering antiviral drugs to adults as appropriate, if they are unlikely to be infected by pandemic influenza considering the status of the outbreak, or if they are diagnosed as influenza B using a quick diagnosis kit.

- The effectiveness of Tamiflu against seasonal influenza has not been identified after 48 hours of the manifestation of symptoms. Therefore, physicians will refrain from administering Tamiflu in such cases for the effective use of Tamiflu. Similarly, for pandemic influenza, it is not recommended to administer Tamiflu after 48 hours of the manifestation of symptoms, though research must be conducted during the actual outbreak.

### (3) Administration in the case of extensive infection

- In the case of extensive infection, (suspected) patients will be generally treated with Tamiflu within 48 hours of the manifestation of symptoms. The highest priority will be placed on patients who are in serious condition and therefore require hospitalization. Administration to outpatients will be performed in order of priority.

Antiviral drugs will be administered to outpatients in the following order of priority. The priority is subject to partial change depending on the characteristics of the actual pandemic influenza virus.

1. Outpatients categorized as health care workers and workers in social services
  2. Outpatients categorized in the medical high-risk group
  3. Children or elderly outpatients
  4. Adult outpatients
- An outbreak of an influenza pandemic is predicted to occur in multiple waves, each of which is likely to last for about two months. “Health care workers and workers in social services etc.” include individuals involved in medical and social services that may threaten the health and social functions of the general public in the case of a two-month discontinuation.
- 1) Health care workers etc. (Of the following, [the minimum required individuals to sustain essential operations]??)

Principle: Individuals involved in medical services that may threaten the lives of the general public in the case of discontinuation

e.g. Health care workers; ambulance staff; drug manufacturers and merchandisers

Note: Of the above, individuals who are likely to contact (suspected) pandemic influenza patients directly in an early stage, such as staff of designated medical institutions for infectious diseases, staff of high-fever outpatient departments and ambulance staff, would receive the administration first.

- 2) Workers in social services etc. (Of the following, [the minimum required individuals to sustain essential operations]??)

- i) Security

Principle: Individuals involved in social services that may threaten social security and order in the case of discontinuation

e.g. Firefighters, police officers, self defense force members, coast guard officers, reformatory officers

ii) Utilities

Principle: Individuals involved in social services that may threaten the minimum quality of life in the case of discontinuation

e.g. Staff of electricity, water, gas and oil utilities; food merchandisers

iii) Crisis management at the central and local governments

Principle: Individuals involved in social services that may threaten the minimum quality of life and social order in the case of discontinuation

e.g. Diet members, local council members, governors, mayors, central and local government officials involved in crisis management

Note: Of the above, individuals who are likely to contact (suspected) pandemic influenza patients directly in an early stage, such as staff of quarantine stations, immigration authorities, customs, health centers and other public health agencies, would be receive the administration first.

iv) Information provision to sustain the minimum quality of life

Principle: Individuals involved in services that may threaten social order due to lack of information in the case of discontinuation

e.g. Members of press, important network services and management

v) Transportation

Principle: Individuals involved in the transport of supplies required to sustain electricity, water, gas, oil, food and other utility services

e.g. Staff of railroad, road, cargo, air and sea transportation



#### **4. Zanamivir hydrate (product name: Relenza)**

##### **(1) Stockpile of Relenza**

- The WHO recommends treatment of pandemic influenza with neuraminidase inhibitor drugs, which include Tamiflu, an oral internal medicine, and Relenza, an oral inhalant. The governments of Japan and other countries are mainly stockpiling Tamiflu because it is easier to administer to infants and the elderly. However, it has been identified that some avian flu virus strains are resistant to Tamiflu but sensitive to Relenza. Therefore, the Japanese government also stockpiles Relenza for crisis management reasons, in case of the occurrence of Tamiflu-resistant virus in Japan.

##### **(2) National stockpile of Relenza**

- Relenza is an inhalant and is therefore more complicated to use than oral internal medicines. In addition, its production and domestic distribution are smaller than Tamiflu. Therefore, the first line drug for the treatment of pandemic influenza will be Tamiflu, and the national stockpile of Relenza will only be used if the pandemic virus proves tolerant to Tamiflu but sensitive to Relenza. In this case, the administration of Relenza will be provided in the same order of priority as in the case of Tamiflu shortage.

